CLINICAL VIGNETTE

Tumor Flare Reaction Syndrome in Lymphoma

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Case Report

A 71-year-old woman was diagnosed with stage IVA, grade 3 follicular lymphoma after presenting with palpable cervical lymphadenopathy. She had bone marrow involvement by lymphoma. She was treated with bendamustine-rituximab for progressive disease and achieved a complete response. Upon her second lymphoma progression, she was treated with dose-adjusted EPOCH-rituximab and achieved a partial and relatively short-lived response. At the time of her third progression, she refused to be considered for high dose therapy and autologous stem cell transplant. Repeat lymph node biopsy did not show large cell transformation. She was treated with lenalidomide. During the first cycle of lenalidomide, she developed low-grade fevers, leukocytosis, and tender peripheral lymph node enlargement on physical exam. Her white blood cell count was 17.1 thousand/μL with a differential of neutrophils 12%, bands 22%, lymphocytes 48%, monocytes 8%, and eosinophils 8%. There was no evidence of infection. PET-CT scan showed interval enlargement of her lymphadenopathy by approximately 20%. There was concern for possible rapid progression of her lymphoma. However, she was suspected to more likely have tumor flare reaction and was continued on lenalidomide. Within 1 month, her symptoms resolved and leukocytosis normalized. Subsequent PET-CT scan showed a complete response with no lymphadenopathy. She remains without evidence of disease on lenalidomide therapy 4 years out from its initiation.

Discussion

Tumor flare reaction (TFR) is an immune reaction first described in patients with chronic lymphocytic leukemia (CLL) being treated with immunomodulatory therapy, specifically lenalidomide and thalidomide.[1,2] TFR typically develops in the first few weeks of therapy and manifests with a rapid increase in size of tender malignant lymph nodes. There is also an association with low-grade fever, lymphocytosis, rash and bone pain.[1,2] Awareness of TFR is important as it can be mistaken for cancer progression leading to premature discontinuation of therapy.

Lenalidomide was originally found to have activity in multiple myeloma and myelodysplastic syndrome (MDS). A phase II clinical trial of lenalidomide in relapsed or refractory CLL also revealed promising activity. Although not seen in myeloma or MDS, TFR was reported in as many as 58% of CLL patients on this study.[3] TFR began as early as the first 24 hours and lasted about 2 weeks. Patients were managed with ibuprofen and morphine if needed. Prophylactic prednisone was later tested in these patients and found to delay the onset and reduce the severity of TFR but not reduce the incidence. None of the CLL patients with TFR required discontinuation of lenalidomide therapy or reduction in dose. Subsequent analysis of this patient population revealed a possible positive correlation between TFR and response, with a complete response rate of 23% in patients with TFR and 7% in patients without TFR.[2] There was no difference in progression free survival between patients who did and did not have TFR.

Since the initial description of TFR in CLL, TFR has been reported in other types of lymphoma treated with lenalidomide. A phase II clinical trial of lenalidomide in relapsed or refractory indolent non-Hodgkin's lymphoma reported an overall response rate of 23%.[4] TFR occurred in 17% of patients with small lymphocytic leukemia and 5% (1 of 22 patients) of patients with indolent follicular lymphoma. In another phase II trial of relapsed or refractory diffuse large B-cell lymphoma, mantle cell lymphoma, grade 3 follicular lymphoma, or transformed lymphoma, lenalidomide yielded on overall response rate of 35% with a TFR incidence of 3%.[5] TFR has also been reported in refractory classic Hodgkin's lymphoma (HL) treated with lenalidomide. A case series of 3 patients with HL found that the TFR resembled early cancer progression but were followed by clinical responses with continuation of therapy.[6] This phenomenon of TFR has been described as pseudo-progression in which the tumor increases in size but ultimately responds to the therapy. Awareness of TFR has led to efforts to modify imaging response criteria to prevent premature declaration of progressive disease when response is underway.[1]

The mechanism by which lenalidomide causes TFR has not been fully elucidated but is generally understood as being a pro-inflammatory effect. Preclinical studies have shown lenalidomide decreases pro-survival cytokines such as tumor necrosis factor alpha and interleukin-6 and activates T cells and natural killer (NK) cells, inducing apoptosis in tumor cells.[1,3] Having an adequate amount of NK cells was associated with TFR intensity and response to therapy.[2] Lenalidomide has also been shown to upregulate B cell activation markers on tumor cells, potentially increasing immunogenicity to T cells.[7] These factors suggest lenalidomide modulates the immune system to exert its anti-tumor effect, sometimes resulting in this TFR phenomenon.

In conclusion, tumor flare reaction is an immune reaction caused by immunomodulatory therapy resulting in a clinical

syndrome of rapid growth of tender lymphadenopathy, low-grade fever, lymphocytosis, and rash. Although initially described in CLL, TFR was later noted in other types of non-Hodgkin's lymphoma as well as Hodgkin's lymphoma treated with lenalidomide, albeit at a lower incidence. Generally, lenalidomide does not need to be dose reduced or discontinued for TFR and can be managed with anti-inflammatory therapies if needed. It is important to recognize TFR since it can mimic early progression of cancer and lead to premature discontinuation of therapy, which would be unfortunate given that patients with TFR may have a greater chance of benefit from therapy.

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